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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of	:	William S. Brusilow
Serial No.	:	10/758,415
For	:	TREATMENT OF POLYGLUTAMINE DISORDERS CAUSED BY EXPANDING GENOMIC CAG NUCLEOTIDES
Filed	:	January 16, 2004
TC/A.U.	:	1614
Examiner	:	Zohreh Vakili
Docket No.	:	2930-109
Customer No.	:	6449
Confirmation No.	:	5654

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

February 13, 2009

APPELLANT'S APPEAL BRIEF UNDER 37 C.F.R. §41.37

Sir:

The following comprises the Patent Owner's Brief on Appeal from the Office Action dated May 5, 2008, in which claims 1-5, 10-11 and 21, were finally rejected. A Notice of Appeal was filed on August 5, 2008. This Appeal Brief is accompanied by the required Appeal fee set forth in 37 C.F.R. § 41.20(b)(2), and is being timely filed on February 12, 2009 along with a 4 month extension of time.

I.

REAL PARTY IN INTEREST

The owner of the above-referenced patent and the real party in interest in this appeal is Odessa Pharma, Chevy Chase, Maryland, USA.

II.

RELATED APPEALS AND INTERFERENCES

The Patent Owner is unaware of any other appeals or interferences related to the subject matter of this appeal.

III.

STATUS OF CLAIMS

The rejection of claims 1-5, 10-11 and 21 is being appealed. Claims 1 and 21 are independent with claims 2-5 and 10-11 depending directly from claim 1. Claims 6-9 and 12-20 are withdrawn. No claims are allowed. The appealed claims are reproduced in the Appendix attached hereto.

IV.

STATUS OF AMENDMENTS

Claim 20 was amended in the response to the non-final rejections, which was filed on February 5, 2007 and new claim 21 was added to the application. No amendments were made in response to the final rejection mailed May 5, 2008. Therefore, it is believed that all amendments have been entered.

V.
SUMMARY OF THE CLAIMED SUBJECT MATTER

A number of neurodegenerative polyglutamine diseases are characterized by expanded genomic CAG sequences resulting in the synthesis and accumulation of polyglutamine tracts in brain proteins of unknown function that are responsible for the neurologic problem. The CAG codon is translated into glutamine (Q). Proteins with expanded polyglutamine domains aggregate and aggregation is a pathologic hallmark of the polyglutamine repeat diseases (page 1, lines 16-23). These polyglutamine length-dependent properties may arise from the ability of long polyglutamine domains to adopt unique three-dimensional conformations and serve to confer the disease proteins with a pathologic gain-of-function (page 2, lines 1-5). All diseases in the CAG repeat family show genetic anticipation, meaning the disease usually appears at an earlier age and increases in severity with each generation. Genetic anticipation is linked to increasing numbers of CAG repeats, which result from expansion of the unstable CAG sequence when reproductive cells divide to form eggs and sperm. In general, neurodegenerative disorders are progressive (i.e., their symptoms are not apparent until months or more commonly years after the disease has begun), and caused by an initial reduction of neuronal function, followed by a complete loss of function upon neuronal death (page 2, lines 7-14).

Currently, physicians prescribe a number of medications to help control emotional and movement problems associated with polyglutamine disorders caused by

expanded genomic CAG nucleotides. Such medications include antipsychotic drugs, such as haloperidol, or other drugs, such as clonazepam, to alleviate choreic movements and also to help control hallucinations, delusions, and violent outbursts; fluoxetine, sertraline, nortriptyline, or other compounds may be prescribed for depression. Tranquilizers can help control anxiety and lithium may be prescribed to combat pathological excitement and severe mood swings. However, while medicines may help keep clinical symptoms under control, there is currently no approved treatment to stop or reverse the course of the disease. (Page 5, lines 1-10)

The present invention is directed to a method for treating polyglutamine disorders caused by expanded genomic CAG nucleotides by reducing the availability of free glutamine in astrocytes (page 7, lines 4-6). Glutamine is supplied to neurons by astrocytes via the glutamine-glutamate cycle. Astrocytes are the only cells in the brain rich in glutamine synthetase (page 7, lines 22-23). Reducing the availability of free glutamine prevents or reduces the biosynthesis of toxic proteins (page 7, lines 4-9). The present inventors have found that L-methionine S-sulfoximine, L-ethionine S-sulfoximine, and glufosinate inhibit glutamine synthetase (page 8, lines 5-21) and branched chain α-keto acids derived from leucine, isoleucine or valine reduce the availability of glutamate in the brain thereby reducing the availability of glutamine for the synthesis of polyglutamine proteins (page 8, line 22 to page 9, line 11).

Independent claim 1 is directed to a method for treating a polyglutamine disease (page 7, lines 4-9), comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and

branched chain α-keto acids derived from leucine, isoleucine or valine (page 1, lines 7-10 and page 7, lines 10-12), to a patient in need of such treatment.

Independent claim 21 is directed to a method for treating a polyglutamine disease caused by expanded genomic CAG nucleotides (page 1, lines 16-21), comprising administering L-methionine S-sulfoximine (page 8, lines 5-16) to a patient suffering from a polyglutamine disease selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy (page 1, lines 16-23).

VI.
GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first issue on appeal is whether the invention claimed in claims 1-5 and 21 is anticipated under 35 USC §102(b) by Apostolakis et al., *Brain Research Bulletin*, vol. 23, pp. 257-262 (1989).

The second issue on appeal is whether the invention claimed in claims 1-5 and 21 is anticipated under 35 USC §102(b) by Ginefri-Gayet et al., *Pharmacology Biochemistry and Behavior*, vol. 43, pp. 173-179 (1992).

The third issue on appeal is whether the invention claimed in claims 10 and 11 is anticipated under 35 USC §102(b) by Liedtke et al. (U.S. Pub. No. 20030013650 A1).

VII.

ARGUMENTS

Claims 1-5 and 21 are not anticipated under 35 USC §102(b) by Apostolakis et al., *Brain Research Bulletin*, vol. 23, pp. 257-262 (1989) because claims 1-5 and 21 recite subject matter not disclosed by the cited prior art.

Apostolakis discloses that MSO is a centrally acting neurotoxin with convulsive properties. The office action dated May 5, 2008 indicates on page 3 that the examiner does not agree with this statement. Applicants point out the first sentence on page 257 of Apostolakis which states that "[M]ethionine sulfoximine (MSO) is a centrally acting neurotoxin with convulsive properties; it has been used for a long time as a tool for the experimental study of epilepsy (20)". Apostolakis also teaches that MSO can cause deformation, atrophy, loss of striation of muscle fibers, fibrosis and degeneration of Purkinje cells in the cerebellum. Apostolakis concludes that administration of MSO to rabbits in addition to the known convulsive effects may also be responsible for hind leg myopathy. The MSO dosage used by Apostolakis was 3-8 mg/kg body weight. Apostolakis does not suggest or disclose that MSO can be used to treat polyglutamine diseases such as Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy and in view of the undesirable side effects discussed in Apostolakis (i.e. deformation, atrophy, loss of striation of muscle fibers, fibrosis and degeneration of Purkinje cells in the cerebellum) one skilled in the art would not be motivated to administer MSO to patients with a polyglutamine disease.

The applicant respectfully points out that the present claims are directed to a method for treating a polyglutamine disease which is not disclosed or suggested by

Apostolakis. The composition and kit claims were withdrawn from consideration in view of applicant's election of group I for examination in the present application and are not involved in this appeal. Though Apostolakis indicates that MSO suppresses the formation of glutamine and glutamate, Apostolakis also states that "[M]ethionine sulfoximine (MSO) is a centrally acting neurotoxin with convulsive properties" (page 257, left column) and that "[F]ollowing the IV MSO administration, the animals became hyperactive and exhibited increased hind leg muscle tonus at 2 hr; at 4-5 hr tetanus-like seizures started..." (page 259, left column). Apostolakis also states in the paragraph bridging pages 260-261 that "[I]n conclusion, administration of small does of MSO to rabbits except for their already known convulsive effects, may also be responsible for hind leg myopathy (rigid paralysis with histological findings resembling myositis)". In view of the numerous undesired effects caused by MSO (convulsant, neurotoxin, etc.) discussed in the cited prior art, applicants contend that not only does the cited prior art fail to anticipate the presently claimed method for treating a polyglutamine disease, but the cited prior art teaches away from administering MSO to any patients for therapeutic purposes. Therefore, applicants contend that Apostolakis does not disclose a method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine. Since Apostolakis does not teach a method for treating a polyglutamine disease as recited in the present claims, applicants request that this rejection be withdrawn.

Claims 1-5 and 21 are not anticipated under 35 USC §102(b) by Ginefri-Gayet et al., *Pharmacology Biochemistry and Behavior*, vol. 43, pp. 173-179 (1992) because claims 1-5 and 21 recite subject matter not disclosed by the cited prior art.

Ginefri-Gayet discloses that MSO, when administered at a convulsant dose (100-200 mg/kg body weight administered intraperitonealy or 50-75 µg per rat administered by ICV injection) induces a decrease in body temperature. Ginefri-Gayet indicates that MSO elicited a time dependent regional perturbation of 5-HT metabolism which could be due to the marked rise in ammonia levels caused by the irreversible inhibition of the activity of glutamine synthetase. Ginefri-Gayet suggests that the 5-HT receptor plays a role in MSO elicited hypothermia in the rat. Ginefri-Gayet does not suggest or disclose that MSO can be used to treat polyglutamine diseases such as Huntington's disease, spinocerebellar ataxia, or spinobulbar muscular atrophy and in view of the undesirable side effects (hypothermia and convulsions), one skilled in the art would not be motivated to treat patients with polyglutamine diseases with MSO in view of the disclosure in Ginefri-Gayet.

The applicant respectfully points out that the present claims are directed to a method for treating a polyglutamine disease which is not disclosed or suggested by Ginefri-Gayet. The composition and kit claims were withdrawn from consideration in view of applicant's election of group I for examination in the present application and are not involved in this appeal. Ginefri-Gayet indicates that MSO is a convulsant molecule that induces a decrease in body temperature (page 173, left column). Ginefri-Gayet states on page 178, right column that "[I]njection of MSO into the third ventricle, allowing

the drug to interact more directly not only with thermoregulatory centers in the hypothalamus but also with brainstem and midbrain neuronal structures, led to a rapid decrease of body temperature, reaching its maximum value during the course of the 0200-0230 h period following administration of MSO". Thus, Ginefri-Gayet discloses that MSO elicits hypothermia at a dose of 50-75 µg/ 10 µl. In view of the numerous undesired effects caused by MSO (hypothermia, convulsant, neurotoxin) discussed in the prior art, applicants contend that not only does the cited prior art fail to anticipate the presently claimed method for treating a polyglutamine disease, but the cited prior art teaches away from administering MSO to any patients for therapeutic purposes. Therefore, applicants contend that Ginefri-Gayet does not disclose a method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine. Since Ginefri-Gayet does not teach a method for treating a polyglutamine disease as recited in the present claims, applicants request that this rejection be withdrawn.

Claims 10 and 11 are not anticipated under 35 USC §102(b) by Liedtke et al. (U.S. Pub. No. 20030013650 A1) because claims 10-11 recite subject matter not disclosed by the cited prior art.

Liedtke discloses an ion channel which is involved in osmoregulation and mechanoreception in vertebrates. The only mention of MSO in Liedtke is in paragraph 207 which discusses mammalian expression vectors such as a glutamine synthetase/ methionine sulfoximine co-amplification vector such as pEE14. There is no disclosure regarding the administration of MSO or a second compound which inhibits aggregate formation, inhibits transglutaminase, inhibits caspase, or is neuroprotective for the treatment of polyglutamine diseases. In addition, there is no disclosure in Liedtke regarding a method for treating a polyglutamine disease by administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine in combination with a second compound selected from the group consisting of Congo red, cystamine, cysteamine, minocycline, ethyl eicosapentaenoate, and riluzole. Claims 10 and 11 depend directly or indirectly from claim 1 which recites a method for treating a polyglutamine disease. Since there is no disclosure in Liedtke regarding the treatment of polyglutamine diseases as recited in the present claims, applicants request that the examiner's decision be reversed and this rejection be withdrawn.

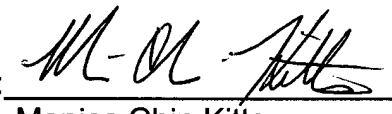
Conclusion

For all of the above noted reasons, it is strongly contended that certain clear differences exist between the present invention as claimed in claims 1- 5, 10-11 and 21 and the prior art relied upon by the Examiner. It is further contended that these differences are more than sufficient evidence that the present invention is not anticipated by the cited prior art.

This final rejection being in error, therefore, it is respectfully requested that this honorable Board of Patent Appeals and Interferences reverse the Examiner's decision in this case and indicate the allowability of claims 1-5, 10-11 and 21.

In the event that this paper is not being timely filed, the Patent Owner respectfully petitions for an appropriate extension of time. Please charge any fee or credit any overpayment pursuant to 37 §C.F.R. 1.16 or §1.17 to Deposit Account No. 02-2135.

Respectfully submitted,

By: 

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VIII.

APPENDIX OF CLAIMS ON APPEAL

1. A method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, to a patient in need of such treatment.

2. The method according to claim 1, wherein said polyglutamine disease is selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy.

3. The method according to claim 1, wherein said compound is L-methionine S-sulfoximine or L-ethionine S-sulfoximine administered orally, intravenously, or intrathecally.

4. The method according to claim 1, wherein said L-methionine S-sulfoximine or L-ethionine S-sulfoximine is administered intrathecally at a dosage between 1.0-5.0 mg/kg per 6-10 days.

5. The method according to claim 1, wherein said L-methionine S-sulfoximine or L-ethionine S-sulfoximine is administered orally or intravenously at a dose between 2.0-

10.0 mg/kg per 6-10 days.

Claims 6-9 were withdrawn and are not involved in this appeal.

10. The method according to claim 1, further comprising administering a second compound which inhibits aggregate formation, inhibits transglutaminase, inhibits caspase, or is neuroprotective.

11. The method according to claim 10, wherein said second compound is selected from the group consisting of Congo red, cystamine, cysteamine, minocycline, ethyl eicosapentaenoate, and riluzole.

Claims 12-20 were withdrawn and are not involved in this appeal.

21. A method for treating a polyglutamine disease caused by expanded genomic CAG nucleotides, comprising administering L-methionine S-sulfoximine to a patient suffering from a polyglutamine disease is selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy.

IX.

Evidence Appendix

None

X.

RELATED PROCEEDINGS APPENDIX

None